1103326-0502

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**



| | |
|---|---|
| Applicants | : Cotton et al. |
| Serial No. | : 10/672,936 |
| Filed | : 25 September 2003 |
| For | : NOVEL FORM OF S-OMEPRAZOLE |
| Examiner | : Aulakh, Charanjit |
| Group Art Unit | : 1625 |

**CERTIFICATE OF TRANSMISSION UNDER 37 C.F.R. 1.8**

I hereby certify that this paper is being facsimile-transmitted to the U.S. Patent and Trademark Office on 19 April 2007 at the facsimile number 571-273-8300.

John M. Genova — 32,224
Agent Name — PTO Reg. No.

Signature — 19 April 2007
Date of Signature

**MAIL STOP APPEAL BRIEF – PATENTS**
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

**67 PAGES (TOTAL)**

**AMENDED**

**BRIEF FOR APPELLANT**

Sir:

A Notification of Non-Compliant Brief ("Notification") was mailed 23 March 2007 in the referenced application. In response thereto, Applicants submits this amended Brief within one-month of the mailing date of the Notification. Accordingly, an extension of time is not necessary.

Applicants appeal the final rejection, mailed 10 August 2006, of claims 1 and 2. A Notice of Appeal was mailed on 8 December 2006. The Commissioner is authorized to charge any fee due in connection with this appeal to Deposit Account No. 23-1703.

## I. REAL PARTY IN INTEREST

The real party in interest is the assignee: AstraZeneca AB (Assignment at Reel 010098, Frame 0174; Change of Name at Reel 012647/0602).

## II. RELATED APPEALS AND INTERFERENCES

No related appeals or interferences are pending. However, there is a pending patent litigation in which the grandparent of the referenced application, i.e., US 6,369,085 (the "'085 patent"), is one of the patents-in-suit. The issue involving the '085 patent is one of patent infringement.

## III. STATUS OF CLAIMS

The original application contained 16 claims, i.e., claims 1-16. By a Preliminary Amendment filed concurrently with the application, claims 2 and 14 were amended, claims 3-13, 15 and 16 were canceled and new claims 17 and 18 were added. Therefore, upon entry of the Preliminary Amendment and prior to any substantive examination of the claims, claims 1, 2, 14, 17 and 18 were pending.

Claims 1, 2, 14, 17 and 18 were rejected twice and a first final Office Action issued 29 April 2005. In response to the first final Office Action, a Request for Continued Examination ("RCE") and an Amendment were filed 28 October 2005. Subsequent to the RCE, the claims were rejected in a non-final Office Action mailed 21 November 2005. Claims 14, 17 and 18 were canceled in the response to the non-final Office Action, thus leaving compounds claims 1 and 2 as the only pending claims, which remained rejected in a second final Office Action, mailed
10 August 2006.

The final rejection of claims 1 and 2 is appealed.

## IV. STATUS OF AMENDMENTS

No amendment has been filed subsequent to the second final Office Action of 10 August 2006.

## V. SUMMARY OF CLAIMED SUBJECT MATTER

Esomeprazole (S-omeprazole) is the (-)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole (specification at p. 1, lines 4-5).

Claim 1 is the only independent claim. As defined by claim 1, the claimed invention is directed to the magnesium salt of S-omeprazole trihydrate (specification at p. 1, lines 6-7). At the time the claimed invention was made, it was not known that the magnesium salt of S-omeprazole occurs in a number of structurally different forms (specification at p. 3, lines 3-4). The compound of the invention is advantageous because it is more stable than the corresponding magnesium salt compounds of S-omeprazole in the prior art and, therefore, it is easier to handle and store (specification at p. 3, lines 11-13).

## VI. THE GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether claims 1 and 2 of the subject application claim the same invention as claims 1 and 2 of the grandparent '085 patent and, therefore, are properly rejected under 35 U.S.C. §101 for statutory double patenting? A copy of the '085 patent is attached hereto as Exhibit A.

## VII. ARGUMENT

A proper rejection under 35 U.S.C. §101 for statutory double patenting requires a determination that the same invention is being claimed twice. *In re Vogel*, 422 F.2d 438, 441 (Fed. Cir. 1970). Such a determination hinges upon the scope of the claims in question. *Id.* at 441; *General Foods Corp.* v. *Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1280 (Fed. Cir. 1992). If the claimed inventions are identical in scope, the proper rejection is under 35 U.S.C. §101. *Miller* v. *Eagle Mfg. Co.*, 151 U.S. 186, 197 (1984).

Although the specification is the primary basis for construing the claims, the prosecution history is also an important resource in ascertaining the scope and meaning of the claims. *Phillips* v. *AWH Corporation*, 415 F.3d 1303, 1317 (Fed. Cir. 2005). With specific regard to the value of the prosecution history to claim construction, the *Phillips* court emphasized that the prosecution history, like the specification, provides evidence of how the PTO and the applicant understood the patent. *Id.* at 1317.

In the pending application, there is no evidence that the Examiner considered the prosecution history of the '085 patent to determine the scope of claims 1 and 2 of the cited '085 patent in relation to claims 1 and 2 of the subject application. Rather, the §101 rejection of record is simply conclusory as suggested by the Examiner's unsupported statement that the "instant claims as well as the claims of the cited patent are identical" (See final Office Action, mailed 10 August 2006, attached hereto as Exhibit B).

In view of *Phillips*, it is respectfully submitted that the prosecution history of the '085 patent must first be consulted to determine how the PTO understood claims 1 and 2 of the '085 patent without which there cannot be a fair and just determination whether claims 1 and 2 of the subject application claim the same invention.

A. Prosecution history of claims 1 and 2 of the '085 patent

This appeal is concerned solely with the propriety of the rejection of compound claims 1 and 2 under 35 U.S.C. §101 for statutory double patenting in view of compound claims 1 and 2 of the grandparent '085 patent.

The '085 patent matured from U.S. Patent Application Serial No. 09/077,719 (the "'719 application"). By a Preliminary Amendment filed 12 November 1999 (attached hereto as Exhibit C), original compound claims 1-3 of the '719 application were amended as follows:

1. (Original) The magnesium salt of S-omeprazole trihydrate.

2. (Amended) The magnesium salt of S-omeprazole trihydrate according to claim 1, wherein the compound is in a ~~characterized by being~~ highly crystalline form.

3. (Amended) The magnesium salt of S-omeprazole trihydrate according to claim 1, wherein the compound is characterized by the following major peaks in its X-ray diffractogram: [.]

[continued]

| d-value / Å | Relative Intensity |
|---|---|
| 2.67 | m |
| 2.79 | m |
| 3.27 | m |
| 3.52 | s |
| 3.82 | s |
| 3.96 | vs |
| 4.14 | m |
| 5.2 | m |
| 5.6 | m |
| 6.7 | vs |
| 6.9 | s |
| 8.3 | w |
| 16.6 | vs |

In a non-final Office Action mailed 27 November 2000 (attached hereto as Exhibit D), the claims of the '719 application, including claims 1-3, were rejected for obviousness under 35 U.S.C. §103 and for obviousness-type double patenting in view of several cited references. The Examiner alleged that the cited references disclose some form of a magnesium salt of omeprazole without specifying the water content. Therefore, according to the Examiner, the differences between the claimed invention and the cited references were the recitation of the (-)-enantiomer and trihydrate form. None of the dependent claims were objected to under 37 C.F.R. §1.75(c) as being an improper dependent claim for failing to further limit the subject matter of a previous claim.

As part of the response to the Office Action, a declaration under 35 U.S.C. §1.132 was filed 4 May 2001 (attached hereto as Exhibit E). The declaration was submitted to show that the claimed magnesium salt of S-omeprazole trihydrate is unexpectedly and advantageously more stable than the cited and closest known prior art, i.e., the magnesium salt of S-omeprazole dihydrate.

***Except for claim 3***, the Examiner maintained the §103 and obviousness-type double patenting rejections of record in the subsequent Office Action mailed 5 July 2001 (attached hereto as Exhibit F). With specific regard to claim 3, the Examiner stated:

3. Claims 1, 2, 4, 14, 16-17 are again rejected under 35 USC 103 as being unpatentable over the art of record for reasons of record. Applicants' declaration has been carefully considered. However, the result only applies to hydrate having the specific X-ray powder diffraction value as listed in claim 3. Embracing the limitation of claim 3 into claim 1 would overcome this rejection.

4. Claims 1, 2, 4, 14, 16-17 are again rejected under the judicially created doctrine of obviousness type double patenting as being unpatentable over the patents of record for reasons of record. Embracing claim 3 into claim 1 would overcome this rejection.

5. Claim 3 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

In the Amendment filed 18 September 2001 (attached hereto as Exhibit G), claim 3 was canceled and claim 1 was amended as follows:

1. (Amended) The magnesium salt of S-omeprazole trihydrate, wherein the compound is characterized by the following major peaks in its X-ray diffractogram:

| d-value / Å | Relative Intensity |
|---|---|
| 2.67 | m |
| 2.79 | m |
| 3.27 | m |
| 3.52 | s |
| 3.82 | s |
| 3.96 | vs |
| 4.14 | m |
| 5.2 | m |
| 5.6 | m |
| 6.7 | vs |
| 6.9 | s |
| 8.3 | w |
| 16.6 | vs |

The next Action was a Notice of Allowance which issued 16 November 2001.

B. Prosecution history of claims 1 and 2 of the pending application

Claims 1 and 2 of the subject application correspond to *original* claims 1 and 2, respectively, of the '719 application (See Claims appendix and Exhibit C).

Claims 1 and 2 of the subject application are rejected under 35 U.S.C. §101 for statutory double patenting in view of claims 1 and 2 of the '085 patent. It is alleged that there is no difference in scope between claims 1 and 2 of the subject application and claims 1 and 2 of the '085 patent since both sets of claims are identical and directed to the magnesium salt of S-omeprazole trihydrate.

C. Pending claims 1 and 2 are different in scope than claims 1 and 2 of the '085 patent.

Although the claims of the '719 application were rejected for prior art reasons, the claims of that application were never objected to for formal reason under 37 C.F.R. §1.75(c) which provides that:

> One or more claims may be presented in dependent form, referring back to and further limiting another claim or claims in the same application.

Thus, the prosecution history of the '085 patent establishes that the PTO understood original claim 3 of the '719 application reciting specific X-ray powder diffraction values to be a proper dependent claim referring back to and further limiting claim 1 directed to the magnesium salt of S-omeprazole trihydrate. The fact that claim 3 was not objected to under 35 C.F.R. §1.75(c) is especially noteworthy in view of recent Federal Circuit decisions stating that an applicant must also satisfy the formal requirements of 35 U.S.C. §112, ¶4, before obtaining a patent. *Pfizer Inc.* v. *Ranbaxy Laboratories Ltd.* 457 F.3d 1284, 1292 (Fed. Cir. 2006); *Curtiss-Wright Flow Control Corp.* v. *Velan, Inc.*, 438 F.3d 1374, 1380 (Fed. Cir. 2006). Therefore, the Examiner's present request for evidence showing that the peaks in X-ray diffractogram of the pending claims are different from the peaks recited by claim 1 of the '085 patent is both superfluous and inconsistent in view of the PTO's understanding that claim 3 of the '719 application contained a reference to claim 1 and specified a further limitation in satisfaction of 35 U.S.C. §112, ¶4 (See final Office Action at Exhibit B). Had this not been the case, §608.01(n) of the Manual of Patent Examining Procedure provides that claim 3 should have been

objected to under 37 C.F.R. §1.75(c) for failing to further limit the subject matter of a previous claim.

Furthermore, although the Examiner was persuaded by the comparative data in the §1.132 declaration showing that the claimed magnesium salt of S-omeprazole trihydrate is unexpectedly and advantageously more stable than the cited and closest known prior art, i.e., the Examiner stated that "the result only applies to hydrate having the specific X-ray powder diffraction value as listed in claim 3" (See Exhibit F). Having stated that the comparative data set forth in the declaration under 37 C.F.R. §1.132 relates only to claim 3, the Examiner indicated that "[e]mbracing the limitations of claim 3 into claim 1" would overcome the prior art rejections (See Exhibit F). In the same Office Action, the Examiner stated that, "[c]laim 3 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims." (See Exhibit F).

The quoted statements from the prosecution history of the '085 patent evidence the PTO's position and how the Examiner understood the claimed invention. Specifically, the Examiner understood there to be a difference in scope between original claim 1 directed to the magnesium salt of S-omeprazole trihydrate and original claim 3 referring back to and further limiting claim 1. To advance the '719 application to allowance and to enjoy the benefits conferred by a U.S. patent for allowable subject matter, claim 1 of the '719 application was amended to recite the X-ray powder diffraction values of claim 3 which was then canceled. The §103 and obviousness-type double patenting rejections were withdrawn and the '085 patent was granted.

Since it was the PTO's position that original claim 3 of the '719 application referred back to and further limited the subject matter of claim 1 of the '719 application in satisfaction of 35 U.S.C. §112, ¶4, and the related regulation 37 C.F.R. §1.75(c), then for the same reason claim 1 of the '085 patent must be limited or narrower in scope than claim 1 of the subject application. The PTO cannot now change its position since Applicants previously relied on the PTO and amended the claims accordingly.

## CONCLUSION

A court has the power and obligation to construe as a matter of law the meaning of the language used in the patent claims. *Markman* v. *Westview Instr., Inc.*, 52 F.3d 967 (Fed. Cir. 1995). The prosecution history is relevant to a proper interpretation of the claims. *Id.* at 980.

The prosecution history of the '085 patent evidences that the PTO understood the scope of original claim 1 directed to the magnesium salt of S-omeprazole trihydrate to differ from that of original claim 3 reciting specific X-ray powder diffraction values. It is submitted that the examination of the invention of original claim 1 of the '719 application in the subject application does not negate the precedent established by the PTO: the scope of original claim 3, now claim 1 of the '085 patent, is different from original claim 1 of the '719 application. *A fortiori*, the scope of original claim 3, now claim 1 of the '085 patent, cannot now be considered identical to that of pending claim 1 merely because patentability of the claimed invention is the subject of a different application.

A contrary conclusion such as the §101 rejection of record derogates the "indisputable public records consisting of the claims, the specification and the prosecution history", thereby undermining the public notice function of patents. *Phillips*, 415 F.3d 1303 at 1319, quoting *Southwall Techs. Inc.* v. *Cardinal IG Co.* 54 F.3d 1570, 1578 (Fed. Cir. 1995). Withdrawal of the §101 rejection is requested.

Attached to this Appeal Brief is an appendix containing a copy of the claims involved in the appeal, i.e., claims 1 and 2.

Respectfully submitted,

Dated: 19 April 2007

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Attachments:

1. Claims Appendix
2. Evidence Appendix
3. Related Proceedings Appendix

## CLAIMS APPENDIX

### U.S. Patent Application Serial No. 10/672,936

1. The magnesium salt of *S*-omeprazole trihydrate.

2. The magnesium salt of *S*-omeprazole trihydrate according to claim 1, wherein the compound is in a highly crystalline form.

## EVIDENCE APPENDIX

### U.S. Patent Application Serial No. 10/672,936

Exhibit A: US 6,369,085

Exhibit B: final Office Action, mailed 10 August 2006, in USSN 10/672,936

Exhibit C: Preliminary Amendment, filed 12 November 1999, in USSN 09/077,719, now US 6,369,085

Exhibit D: non-final Office Action, mailed 27 November 2000, in USSN 09/077,719, now US 6,369,085

Exhibit E: Declaration of Frans W. Langkilde, filed 4 May 2001, in USSN 09/077,719, now US 6,369,085

Exhibit F: non-final Office Action, mailed 5 July 2001, in USSN 09/077,719, now US 6,369,085

Exhibit G: Amendment, filed 18 September 2001, in USSN 09/077,719, now US 6,369,085

## RELATED PROCEEDINGS APPENDIX

## U.S. Patent Application Serial No. 10/672,936

**NONE**

**EXHIBIT A**

**US 6,369,085**


(12) **United States Patent**
**Cotton et al.**

(10) **Patent No.: US 6,369,085 B1**
(45) **Date of Patent: Apr. 9, 2002**

(54) **FORM OF S-OMEPRAZOLE**

(75) Inventors: **Hanna Cotton; Anders Krunström; Anders Muttson; Eva Möller**, all of Södertälje (SE)

(73) Assignee: **AstraZeneca AB**, Sodertalje (SE)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/077,719**

(22) PCT Filed: **May 5, 1998**

(86) PCT No.: **PCT/SE98/00974**

§ 371 Date: **Jun. 8, 1998**

§ 102(e) Date: **Jun. 8, 1998**

(87) PCT Pub. No.: **WO98/54171**

PCT Pub. Date: **Dec. 3, 1998**

(30) **Foreign Application Priority Data**

May 30, 1997 (SE) ..... 9702065

(51) **Int. Cl.**[7] ..... **A61K 31/4439; C07D 401/12**
(52) **U.S. Cl.** ..... **514/338; 546/273.7**
(58) **Field of Search** ..... **514/338; 546/273.7**

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| EP | 0247983 | 12/1987 |
| WO | 9427988 | 12/1994 |
| WO | WO 95/01977 | * 1/1995 |
| WO | 9601623 | 1/1996 |
| WO | 9602535 | 2/1996 |

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von Unge, S. et al. "Stereochemical assignment of the enantiomers of omeprazole from X-ray analysis of a fenchyloxylmethyl derivative of (+)-(R)-omeprazole", *Tetrahedron Asymmetry*, vol. 8, No. 12, pp. 1967–1970 (1997).

* cited by examiner

*Primary Examiner*—Jane Fan
(74) *Attorney, Agent, or Firm*—White & Case LLP

(57) **ABSTRACT**

The present invention relates to a novel form of the (-)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, i.e. S-omeprazole. More specifically, it relates to a novel form of the magnesium salt of the S-enantiomer of omeprazole trihydrate. The present invention also relates to processes for preparing such a form of the magnesium salt of S-omeprazole and pharmaceutical compositions containing it. Furthermore, the present invention also relates to new intermediates used in the process.

**12 Claims, 5 Drawing Sheets**

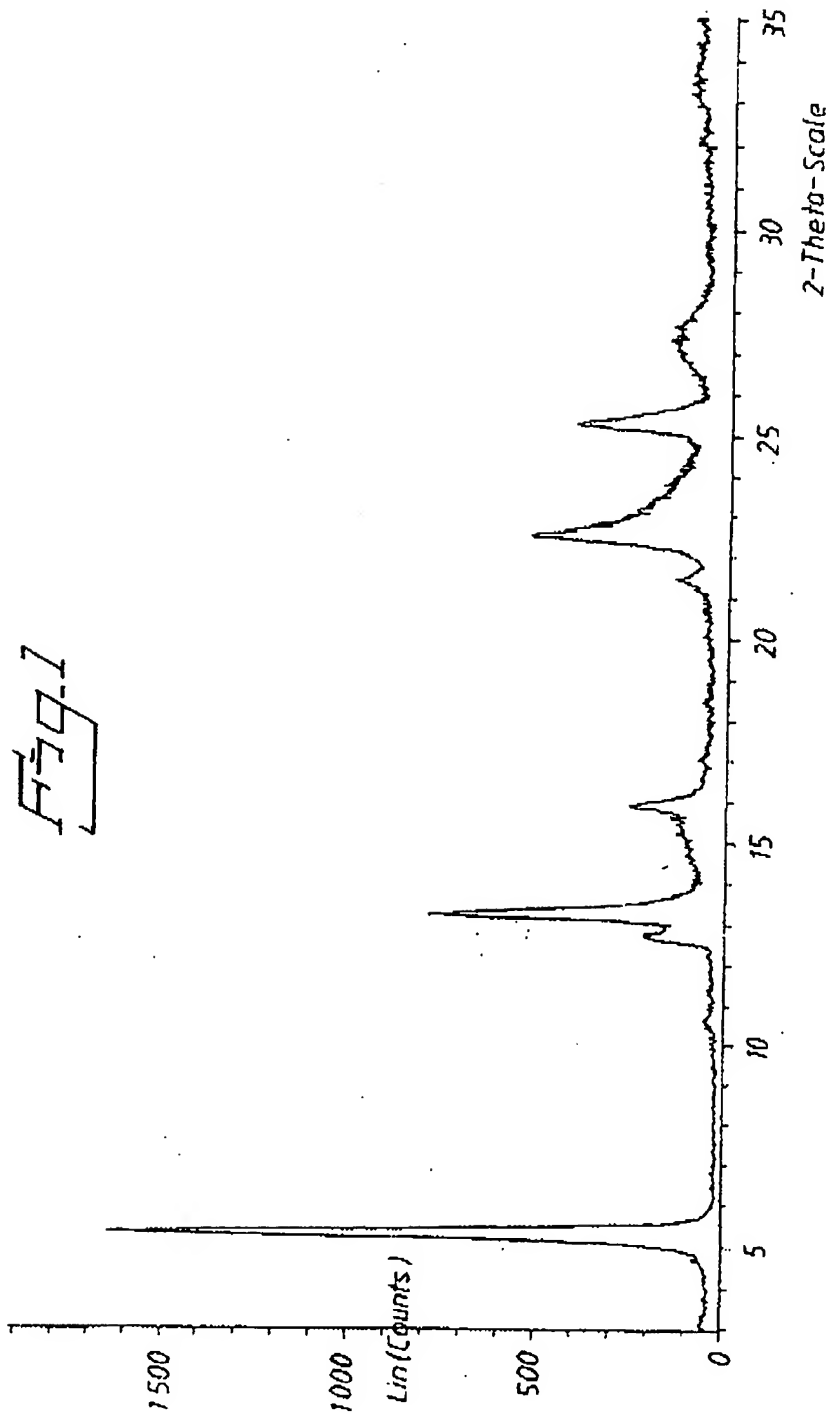


Fig. 1

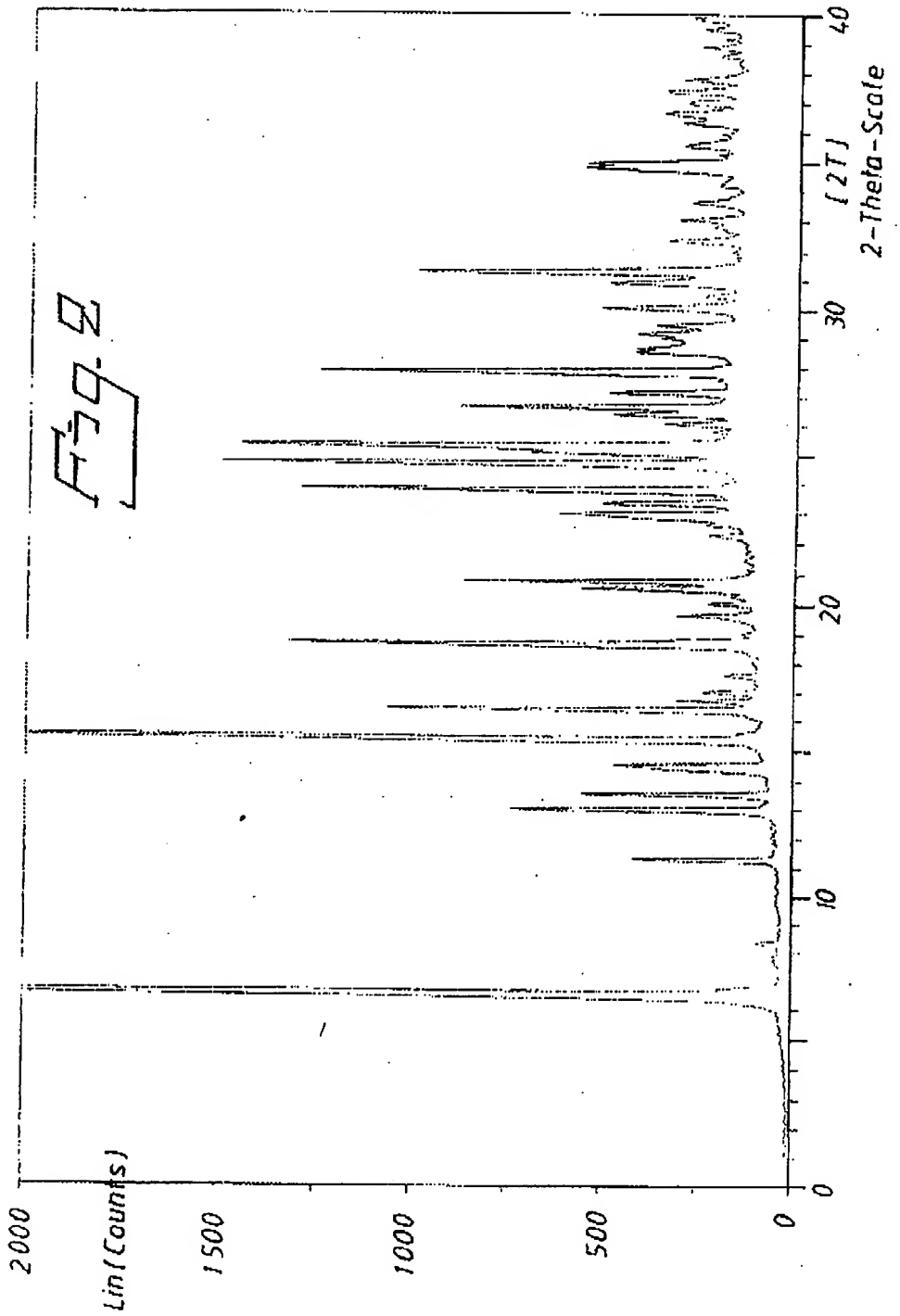
Fig. 2
Lin (Counts)
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1500
1000
500
0
0
10
20
30
40
2-Theta-Scale (2T)

Fig. 3

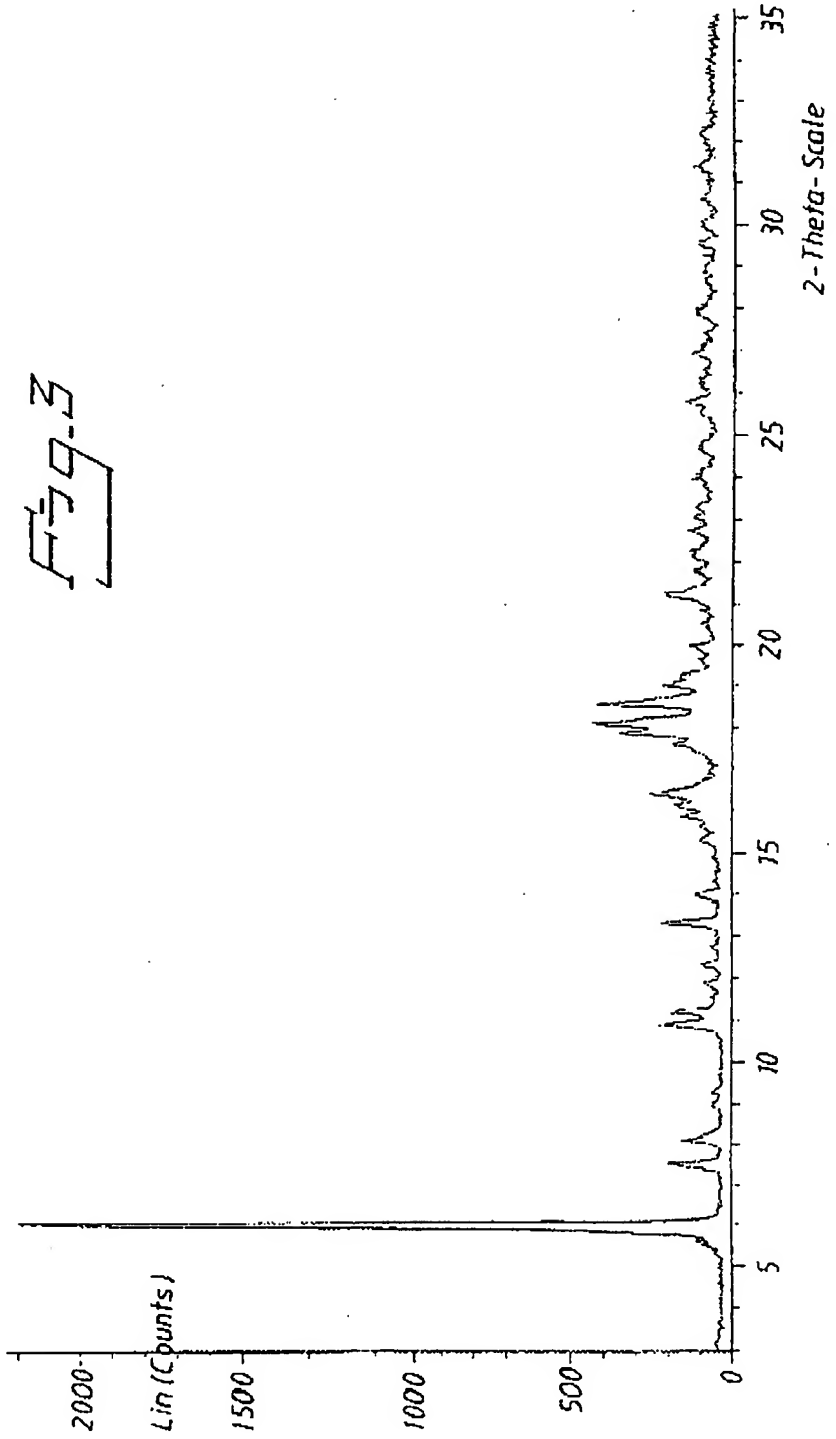
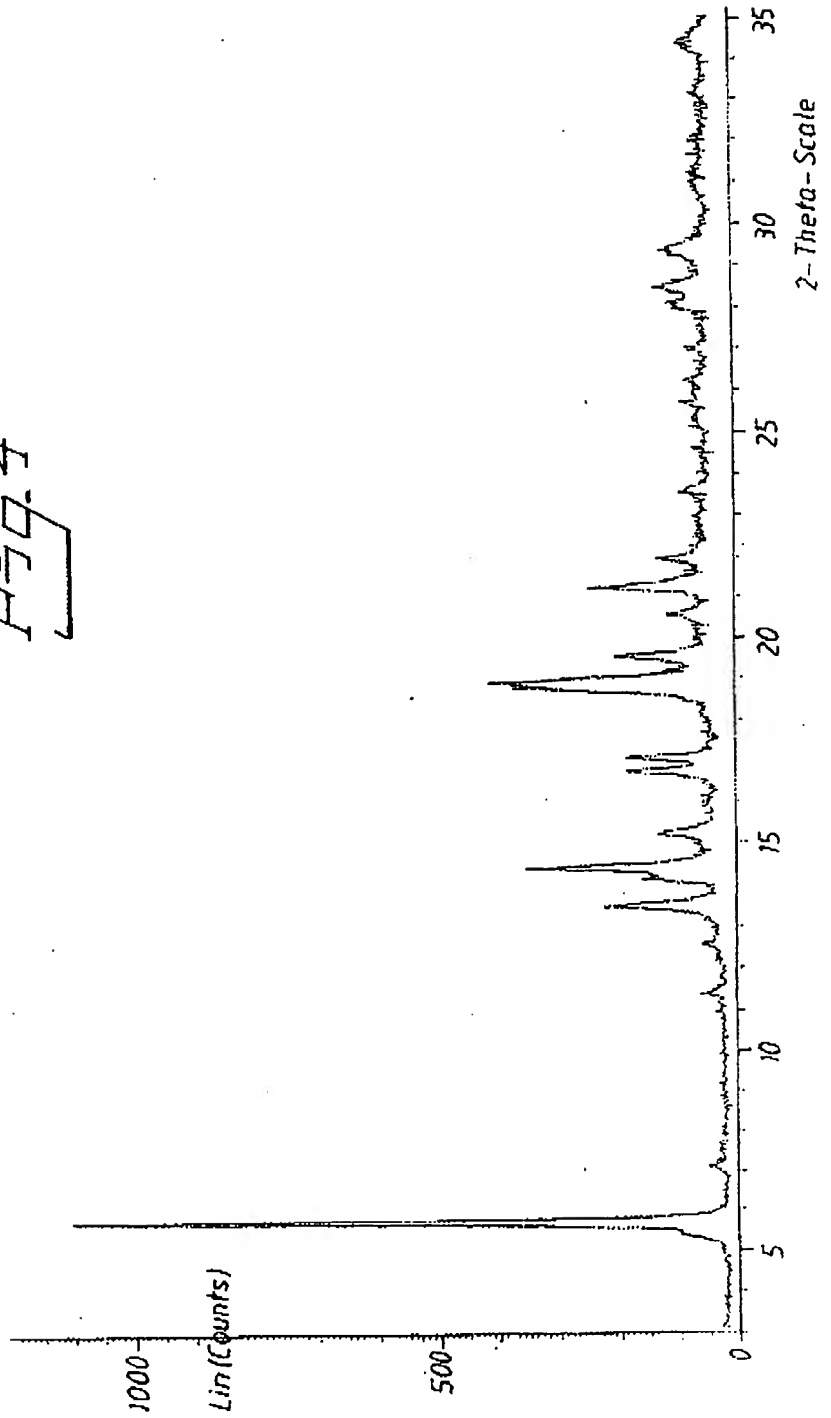


Fig. 4



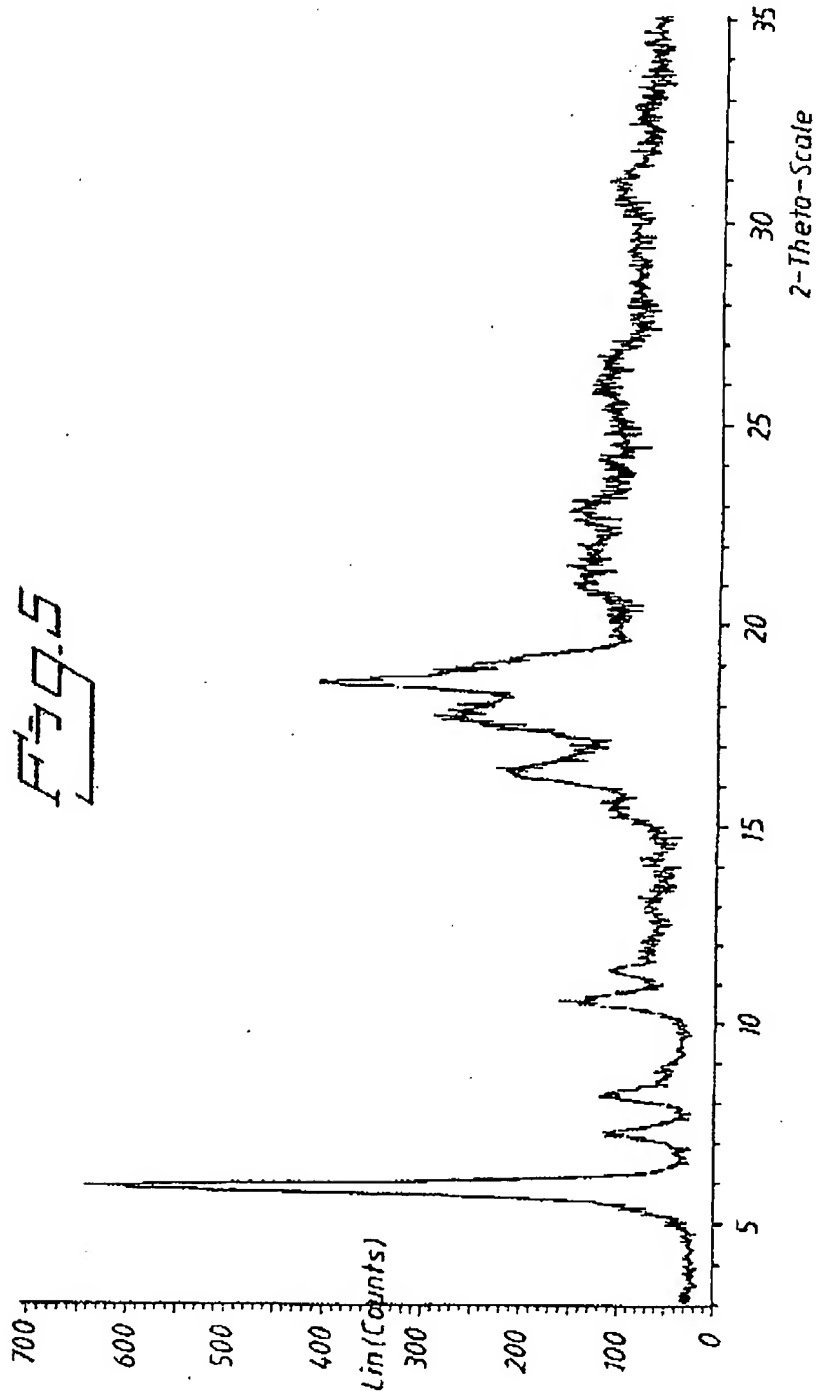

Lin (Counts)
0
100
200
300
400
500
600
700
5
10
15
20
25
30
35
2-Theta-Scale

Fig. 5

# FORM OF S-OMEPRAZOLE

This application is a 371 of PCT/SE98/00974, May 5, 1998 now WO 9854171 Dec. 3, 1998.

## FIELD OF THE INVENTION

The present invention relates to a novel form of the (−)-enantiomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole, i.e. S-omeprazole. More specifically, it relates to a novel form of the magnesium salt of the S-enantiomer of omeprazole trihydrate. The present invention also relates to processes for preparing such a form of the magnesium salt of S-omeprazole and pharmaceutical compositions containing it. Furthermore, the present invention also relates to intermediates used in the process, and their preparation.

## BACKGROUND OF THE INVENTION AND PRIOR ART

The compound 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, having the generic name omeprazole, and therapeutically acceptable salts thereof, are described in EP 5129. The specific alkaline salts of omeprazole are disclosed in EP 124 495. Omeprazole is a proton pump inhibitor, i.e. effective in inhibiting gastric acid secretion, and is useful as an antiulcer agent. In a more general sense, omeprazole may be used for prevention and treatment of gastric-acid related diseases in mammals and especially in man.

Omeprazole is a sulfoxide and a chiral compound, wherein the sulfur atom being the stereogenic center. Thus, omeprazole is a racemic mixture of its two single enantiomers, the R and S-enantiomer of omeprazole, herein referred to as R-omeprazole and S-omeprazole. The absolute configurations of the enantiomers of omeprazole have been determined by an X-ray study of an N-alkylated derivative of the (+)-enantiomer in non-salt form. The (+)-enantiomer of the non-salt form and the (−)-enantiomer of the non-salt form were found to have R and S configuration, respectively, and the (+)-enantiomer of the magnesium salt and the (−)-enantiomer of the magnesium salt were also found to have R and S configuration, respectively. The conditions for the optical rotation measurement for each of these enantiomers are described in WO 94/27988.

Certain salts of single enantiomers of omeprazole and their preparation are disclosed in WO 94/27988. These compounds have improved pharmacokinetic and metabolic properties which will give an improved therapeutic profile such as a lower degree of interindividual variation.

WO 96/02535 discloses a process for the preparation of the single enantiomers of omeprazole and salts thereof, and WO 96/01623 discloses a suitable tableted dosage forms of for instance magnesium salts of R- and S-omeprazole.

## BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows a X-ray powder diffractogram of the magnesium salt of S-omeprazole trihydrate prepared according to the present invention.

FIG. 2 shows a X-ray powder diffractogram of the potassium salt of S-omeprazole prepared and used in the present application (See examples 2 and 3)

FIG. 3 shows a X-ray powder diffractogram of a magnesium salt of S-omeprazole dihydrate prepared and used in the present application (See example 5)

FIG. 4 shows a X-ray powder diffractogram of a magnesium salt of S-omeprazole dihydrate which is a polymorph of the dihydrate shown in FIG. 3 (See Example 6). This magnesium salt of S-omeprazole dihydrate has been prepared and can be used in the preparation of the magnesium salt of S-omeprazole trihydrate according to the present invention.

FIG. 5 shows X-ray powder diffractogram of the magnesium salt of S-omeprazole prepared according to example A in WO 96/01623.



## DESCRIPTION OF THE INVENTION

It has surprisingly been found that the magnesium salt of S-omeprazole occurs in a number of structurally different forms. It is an object of the present invention to provide a substantially pure magnesium salt of S-omeprazole trihydrate, hereinafter referred to as the compound of the invention. This trihydrate can be obtained as a well defined compound. The present invention also provides a process to obtain and a method of differentiating the magnesium salt of S-omeprazole trihydrate from other forms of magnesium salts of S-omeprazole.

The compound of the invention is advantageous because it is more stable than the corresponding magnesium salt compounds in prior art and is therefore easier to handle and store. The compound of the invention is also easier to characterize because it exists in a well defined state. Additionally, the compound of the invention is easier to synthesize in a reproducible manner and thereby easier to handle in a full scale production.

The magnesium salt of S-omeprazole trihydrate obtained according to the present invention is substantially free from magnesium salts of R-omeprazole. The magnesium salt of S-omeprazole trihydrate obtained according to the present invention is also substantially free from other forms of magnesium salts of S-omeprazole, such as the corresponding magnesium salt compounds described in prior art, and dihydrates used in the preparation of the trihydrate compound according to the present invention.

The compound of the invention is characterized by the positions and intensities of the major peaks in the X-ray powder diffractogram, but may also be characterized by conventional FT-IR spectroscopy. These characteristics are not exhibited by any other form of magnesium salt of S-omeprazole and accordingly, the magnesium salt of S-omeprazole trihydrate is easily distinguishable from any other crystal form of the magnesium salt of S-omeprazole disclosed in prior art. The compound of the invention is characterized by being highly crystalline, i.e. having a higher crystallinity than any other form of magnesium salt of S-omeprazole disclosed in the prior art. With the expression "any other form" is meant anhydrates, hydrates, solvates, and polymorphs or amorphous forms thereof disclosed in the prior art. Examples of any other forms of magnesium salt of S-omeprazole includes, but are not limited to, anhydrates, monohydrates, dihydrates, sesquihydrates, trihydrates, alcoholates, such as methanolates and ethanolates, and polymorphs or amorphous forms thereof.

The compound of the invention may also be characterized by its unit cell.

In a further aspect, the present invention provides processes for the preparation of the magnesium salt of S-omeprazole trihydrate which comprises;

a) treating a magnesium salt of S-omeprazole of any form, for example prepared according to procedures known in the art such as Example A in WO 96/01623 which is incorporated herein by reference, with water at a suitable temperature for a suitable time. By a suitable

temperature is meant a temperature which induces the transformation of starting material to product without decomposing any of these compounds. Examples of such suitable temperatures include, but are not limited to, room temperature and above. By a suitable time is meant a time that results in high conversion of the starting material into product without causing any decomposition of either compounds, i.e. results in a good yield. This suitable time will vary depending on the temperature used in a way well known to people in the art. The higher the temperature, the shorter time is needed to give the desired conversion. The amount of water is not crucial and will depend on the process conditions used. The magnesium salt of S-omeprazole trihydrate is thereafter separated from the aqueous slurry, for example by filtration or centrifugation and thereafter dried to constant weight; or

b) oxidizing 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole, with an oxidizing agent and a chiral titanium complex, optionally in the presence of a base. The oxidation is carried out in an organic solvent, for example toluene or dichloromethane.

The crude product is converted to the corresponding potassium salt by treatment with a potassium source, such as methanolic potassium hydroxide or methanolic potassium methylate, followed by isolation of the formed salt.

The resulting potassium salt of S-omeprazole is thereafter converted to the corresponding magnesium salt by treatment with a magnesium source, such as magnesium sulfate in a lower alcohol, such as methanol. The solution is optionally filtered and the precipitation is initialized by addition of a non-solvent such as acetone. The product is filtered off and optionally washed with water and further processed as is described in a) above. Alternatively, the potassium salt may be treated with a magnesium source, such as magnesium sulfate in water, and isolation of the magnesium salt of S-omeprazole trihydrate, or any other conventional technique for transforming a potassium salt to the corresponding magnesium salt can be used and is within the scope of the present invention.

Yet a further aspect of the present invention is to provide a suitable intermediate used in the preparation of the compound of the invention, as well as a process for its preparation. The potassium salt of S-omeprazole is found to be such a suitable intermediate. The potassium salt of S-omeprazole may also be used as an active component of a pharmaceutical formulation to be used in the treatment of gastrointestinal diseases.

The compound of the invention, i.e. the magnesium salt of S-omeprazole trihydrate, prepared according to the present invention may be analyzed by XRPD, a technique which is known per se.

The amount of water in the magnesium salt of S-omeprazole trihydrate is determined by thermogravimetric analysis, a technique which is known per se.

The compound of the invention is effective as a gastric acid secretion inhibitor, and is useful as an antiulcer agent. In a more general sense, it can be used for prevention and treatment of gastric-acid related conditions in mammals and especially in man, including e.g. reflux esophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. Furthermore, it may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable e.g. in patients on NSAID therapy, in patients with Non Ulcer Dyspepsia, in patients with symptomatic gastro-esophageal reflux disease, and in patients with gastrinomas. The compound of the invention may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre- and postoperatively to prevent aspiration of gastric acid and to prevent and treat stress ulceration. Further, the compound of the invention may be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections and diseases related to these. The compound of the invention may also be used for treatment of inflammatory conditions in mammals, including man.

Any suitable route of administration may be employed for providing the patient with an effective dosage of the magnesium salt of S-omeprazole trihydrate, according to the invention. For example, peroral or parental formulations and the like may be employed. Dosage forms include capsules, tablets, dispersions, suspensions and the like.

It is further provided a pharmaceutical composition comprising the magnesium salt of S-omeprazole trihydrate according to the invention, as active ingredient, in association with a pharmaceutically acceptable carrier, diluent or excipient and optionally other therapeutic ingredients. Compositions comprising other therapeutic ingredients are especially of interest in the treatment of Helicobacter infections. The invention also provides the use of the magnesium salt of S-omeprazole trihydrate of the invention in the manufacture of a medicament for use in the treatment of a gastric-acid related condition and a method of treating a gastric-acid related condition which method comprises administering to a subject suffering from said condition a therapeutically effective amount of the magnesium salt of S-omeprazole trihydrate according to the invention.

The compositions of the invention include compositions suitable for peroral or parental administration. The most preferred route is the oral route. The compositions may be conveniently presented in unit dosage forms, and prepared by any methods known in the art of pharmacy.

In the practice of the invention, the most suitable route of administration as well as the magnitude of a therapeutic dose of the magnesium salt of S-omeprazole trihydrate according to the invention in any given case will depend on the nature and severity of the disease to be treated. The dose, and dose frequency, may also vary according to the age, body weight, and response of the individual patient. Special requirements may be needed for patients having Zollinger-Ellison syndrome, such as a need for higher doses than the average patient. Children and patients with liver diseases generally will benefit from doses that are somewhat lower than the average. Thus, in some conditions it may be necessary to use doses outside the ranges stated below, for example long term treatments may request lower dosage. Such higher and lower doses are within the scope of the present invention. Such daily doses may vary between 5 mg to 300 mg.

In general, a suitable oral dosage form of the compound of the invention may cover a dose range from 5 mg to 300 mg total daily dose, administered in one single dose or equally divided doses. A preferred dosage range is from 10 mg to 80 mg.

The compound of the invention may be combined as the active component in intimate admixture with a pharmaceutical carrier according to conventional techniques, such as the oral formulations described in WO 96/01623 and EP 247 983, the disclosures of which are hereby incorporated as a whole by reference.

Combination preparations comprising the magnesium salt of S-omeprazole trihydrate and other active ingredients may also be used. Examples of such active ingredients include, but are not limited to anti-bacterial compounds, non-steroidal anti-inflammatory agents, antacid agents, alginates and prokinetic agents.

The examples which follow will further illustrate the preparation of the compound of the invention, according to different process routes and including new intermediates. These examples are not intended to limit the scope of the invention as defined hereinabove or as claimed below.

## EXAMPLES

### Example 1

S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt trihydrate

Water (157 kg) was added to the wet crystals of the magnesium salt of S-omeprazole, prepared according to Example 4, below. The mixture was heated to 38° C. with stirring and left for 3 hours. The crystals were filtered off and dried in vacuo. Yield: 31.6 kg

X-ray powder diffraction analysis was performed on a sample of the crystals prepared above according to standard methods, which can be found in e.g. Kitaigorodsky, A. I. (1973), Molecular Crystals and Molecules, Academic Press, New York; Bunn, C. W. (1948), Chemical Crystallography, Clarendon Press, London; or Klug, H. P. & Alexander, L. E. (1974), X-Ray Diffraction Procedures, John Wiley and Sons, New York. The analysis gave the diffractogram depicted in FIG. 1. The main peaks, with positions and relative intensities, have been extracted from the diffractogram in FIG. 1 and is given below in table 1. The relative intensities are less reliable and instead of numerical values the following definitions are used.

| % Relative Intensity | Definition |
|---|---|
| 25–100 | vs (very strong) |
| 10–25 | s (strong) |
| 3–10 | m (medium) |
| 1–3 | w (weak) |
| <1 | vw (very weak) |

Some additional very weak peaks found in the diffractogram have been omitted from table 1.

TABLE 1

Positions and intensities of the major peaks in the XRP-diffractogram of the magnesium salt of S-omeprazole trihydrate.

| d-value / Å | Relative Intensity |
|---|---|
| 2.67 | m |
| 2.79 | m |
| 3.27 | m |
| 3.52 | s |
| 3.82 | s |
| 3.96 | vs |
| 4.14 | m |
| 5.2 | m |
| 5.6 | m |
| 6.7 | vs |
| 6.9 | s |
| 8.3 | w |
| 14.6 | vs |

### Example 2

S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole potassium salt

A solution of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole (15.4 g, 46.8 mmol) in toluene (70 ml) was heated to 50° C. and water (0.05 ml, 2,8 mmol) and D-(−)-diethyl tartrate (2.02 g, 9.82 mmol) were added. The reaction mixture was stirred for 20 minutes. Titanium(IV)isopropoxide (1.34 g, 4.68 mmol) was added and the reaction mixture was stirred for 45 minutes. The mixture was cooled to 30° C. and diisopropylethylamine (0.91 g, 7.01 mmol) was added followed by cumene hydroperoxide (9.52 g, 51.89 mmol). The resultant mixture was stirred at 30° C. for 3 hours. Methanol (40 ml) was added followed by potassium hydroxide (3.05 g, 46.8 mmol) in methanol (30 ml). Seed crystals were added and the reaction mixture was stirred at 35° C. overnight. The precipitated product was filtered off, washed with methanol and toluene and dried in vacuo. Yield: 9.74 g (54%).



### Example 3

S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole potassium salt

Water (157.6 gl) was added to a solution of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole in toluene (370 ml; 211.5 g/l) with a water content of 0.031% (w/w), followed by addition of D-(−)-diethyl tartrate (8.55 ml). The solution was heated to 50° C. and stirred at this temperature for 20 minutes. Titanium(IV) isopropoxide (7.15 ml) was added and reaction was left at 50° C. for 45 minutes. The temperature was lowered to 30° C. and diisopropylethylamine (6.2 ml) was added. Cumene hydroperoxide was added at an appropriate speed to maintain the temperature from 28° C. to 34° C. The temperature was raised to 35° C. after 2 hours and potassium methoxide (24.55 g) in methanol (222 ml) was added. The mixture was filtered after 14 hours and the crystals were washed with methanol:toluene (240 ml; 1:1) and methanol (120 ml) and dried. Yield: 79 g (74%), ee>99.9%. $[\alpha]_D^{20}$=+28.7° (c=1%, water); Assay: 89% is S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole potassium salt (11% is methanol).

1H-NMR (200 MHz, DMSO-d6, δ ppm): 2.23 (s, 3H), 2.24 (s, 3H), 3.71 (s, 3H), 3.75 (s 3H), 4.40 (d, 1H), 4.78 (d, 1H), 6.58 (dd, 1H), 7.00 (d, 1H), 7.35 (d, 1H), 8.25 (s, 1H.

The products from Examples 2 and 3 were analysed using X-ray powder diffraction as described in Example 1 and gave the diffractogram depicted in FIG. 2 and given below in

Table 2. Some additional very weak peaks found in the diffractogram have been omitted from Table 2.

TABLE 2

Positions and intensities of the major peaks in the XRP-diffractogram of the potassium salt of S-omeprazole.

| d-value/Å | Relative intensity | d-value/ (Å) | Relative intensity | |
|---|---|---|---|---|
| 13.6 | vs | 3.52 | m | |
| 10.6 | vw | 3.43 | w | |
| 7.8 | m | 3.38 | w | |
| 6.8 | m | 3.34 | m | |
| 6.5 | m | 3.28 | w | |
| 6.2 | w | 3.20 | m | |
| 6.1 | m | 3.12 | w | |
| 5.8 | s | 3.06 | w | |
| 5.4 | m | 3.03 | w | |
| 5.3 | w | 2.97 | w | α1 = 1.54060 Å |
| 5.2 | w | 2.93 | vw | |
| 5.0 | vw | 2.89 | w | |
| 4.75 | m | 2.85 | m | |
| 4.71 | w | 2.76 | w | |
| 4.52 | w | 2.71 | vw | |
| 4.42 | w | 2.66 | vw | |

TABLE 2-continued

Positions and intensities of the major peaks in the XRP-diffractogram of the potassium salt of S-omeprazole.

| d-value/Å | Relative intensity | d-value/ (Å) | Relative intensity |
|---|---|---|---|
| 4.32 | w | 2.58 | w |
| 4.29 | m | 2.57 | w |
| 3.98 | vw | 2.56 | w |
| 3.92 | w | 2.52 | vw |
| 3.89 | w | 2.47 | vw |
| 3.87 | w | 2.45 | vw |
| 3.81 | w | 2.43 | vw |
| 3.74 | m | 2.40 | vw |
| 3.60 | m | 2.38 | vw |
| 3.55 | m | 2.31 | vw |

Example 4

S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt

Methanol (148 kg) was added to S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole potassium salt (71 kg, methanol content=13%). $MgSO_4 \times 7\ H_2O$ (40 kg) was added to the mixture while stirring. After 70 minutes the mixture was filtered and the filtrate was washed with methanol (46 kg). The solution was concentrated to a volume of 100 liter, acetone (253 kg) was added and the resulting mixture was left for 4 hours. The precipitated product was filtered off, washed with acetone and water. The wet crystals were immediately used as is described in Example 1.

Example 5

S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt dihydrate

5.0 g of the moist product from Example 4 with an approximate dry content of 74%, was dried in vacuum at 35° C. over night to yield 3.58 g (2.68 mmol) of S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt dihydrate, named Form B.

The product was analyzed using X-ray powder diffraction as described in Example 1, and the analyze gave the diffractogram depicted in FIG. 3 and given below in Table 3. Some additional peaks with low intensities found in the diffractogram have been omitted from Table 3.

TABLE 3

Positions and intensities of the major peaks in the XRP-diffractogram of the magnesium salt of S-omeprazole dihydrate, Form B.

| d-value/Å | Relative Intensity |
|---|---|
| 4.19 | m |
| 4.45 | m |
| 4.68 | m |
| 4.79 | s |
| 4.91 | s |
| 4.98 | s |
| 5.1 | m |
| 5.4 | s |
| 5.5 | m |
| 5.6 | m |
| 5.8 | m |
| 6.3 | m |
| 6.7 | s |
| 7.9 | m |

TABLE 3-continued

Positions and intensities of the major peaks in the XRP-diffractogram of the magnesium salt of S-omeprazole dihydrate, Form B.

| d-value/Å | Relative Intensity |
|---|---|
| 8.1 | s |
| 11.0 | m |
| 11.8 | m |
| 14.9 | vs |

Convertion of magnesium salt of S-omeprazole dihydrate to trihydrate

This material was subsequently processed to S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt trihydrate according to the procedure described for the moist substance in Example 1.

Example 6

S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt dihydrate

A methanolic solution of S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt was prepared as is described in Example 4. Such a solution of S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt (1.86 g) in 5 ml methanol was concentrated by evaporation until 1.58 ml methanol remained. Then, a mixture of 1.6 ml water and 6.32 ml aceton was added. The solution was allowed to crystallize during 26 h at room temperature. The resulting crystals were filtered off and dried at 40 °C. under reduced pressure giving 1.17 g of S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt dihydrate, named form A.

The product was analyzed using X-ray powder diffration as described in Example 1 and gave the diffractogram depicted in FIG. 4 and given below in Table 4. Some additional peaks with low intensities found in the diffractogram have been omitted from Table 4.

TABLE 4

Positions and intensities of the major peaks in the XRP-diffractogram of the magnesium salt of S-omeprazole dihydrate, Form A.

| d-value/Å | Relative Intensity |
|---|---|
| 3.04 | s |
| 3.14 | s |
| 3.18 | m |
| 4.05 | s |
| 4.19 | s |
| 4.32 | m |
| 4.54 | s |
| 4.69 | vs |
| 5.2 | s |
| 5.3 | s |
| 5.8 | s |
| 6.2 | vs |
| 6.6 | s |
| 15.5 | vs |

Example 7

S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt trihydrate

22.0 g (29.1 mmol) of S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole

potassium salt was dissolved in 40 mL of water. The solution was seeded with 0,11 g (0,1 mmol) S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt trihydrate. 22 mL (69,6 mmol) of $MgSO_4$ (aq) was added under a 3 h period. The slurry was filtered off and the precipitate was elutriated in water for approximately 30 minutes and the crystals were filtered off and dried (35° C., vacuum).

Yield: 9,15 g (11,6 mmol; 80%). The substance had a purity (HPLC):99,8 area %, Mg content: 3,40% (w/w) and ee: 99,8%.

The product was analyzed using X-ray powder diffraction and the result complies with a FIG. 1 and Table 1.

Reference Example A

S-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole magnesium salt

(The method used is in accordance with the method described in Example A in WO 96/01623)

Magnesium (0.11 g, 4.5 mmol) was dissolved and reacted with methanol (50 ml) at 40° C. with a catalytic amount of methylene chloride. The reaction was run under nitrogen and was finished after five hours. At room temperature a mixture of the two enantiomers [90%(−)-isomer and 10%(+)-isomer] of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1H-benzimidazole (2.84 g, 8.2 mmol) was added to the magnesium methoxide solution. The mixture was stirred for 12 hours whereupon a small amount of water (0.1 ml) was added in order to precipitate inorganic magnesium salts. After 30 minutes stirring, these inorganic salts were filtered off and the solution was concentrated on a rotavapor. The residue was now a concentrated methanolic solution of the enantiomeric mixture (i.e. the title compound contaminated with the (+)-isomer), with an optical purity (enantiomeric excess, e.e.) of 80%. This mixture was diluted with acetone (100 ml) and after stirring at room temperature for 15 minutes, a white precipitate was obtained. Additional stirring for 15 minutes and thereafter filtration afforded 1.3 g (50%) of the title compound as white crystals. Chiral analyses of the crystals and mother liquor were performed by chromatography on an analytical chiral column. The optical purity of the crystals and mother liquor was found to be 98.4 e.e. and 64.4% e.e., respectively. Thus, the optical purity (e.e.) has been enhanced from 80% to 98.4% simply by crystallizing the Mg-salt from a mixture of acetone and methanol. The product was crystalline as shown by powder X-ray diffraction and the magnesium content was 3.44% as shown by atomic absorption spectroscopy. $[\alpha]_D^{20}$=−131.5° (c=0.5%, methanol).

The product was analyzed using X-ray powder diffraction as described in Example 1 and gave the diffractogram depicted in FIG. 5 and given below in Table 5. Some additional very weak peaks found in the diffractograms have been omitted from Table 5.

TABLE 5

Positions and intensities of the major peaks in the XRP-diffractogram shown in FIG. 5.

| d-value/Å | Relative Intensity |
|---|---|
| 2.90 | s |
| 3.41 | s |
| 3.99 | s |
| 4.23 | s |
| 4.79 | vs |
| 5.00 | vs |
| 5.4 | vs |
| 5.7 | s |
| 6.3 | s |
| 6.8 | s |
| 7.8 | s |
| 8.4 | vs |
| 10.8 | s |
| 12.2 | s |
| 15.1 | vs |

What is claimed is:

1. The magnesium salt of S-omeprazole trihydrate, wherein the compound is characterized by the following major peaks in its X-ray diffractogram:

| d-value / Å | Relative Intensity |
|---|---|
| 2.67 | m |
| 2.79 | m |
| 3.27 | m |
| 3.52 | s |
| 3.82 | s |
| 3.96 | vs |
| 4.14 | m |
| 5.2 | m |
| 5.6 | m |
| 6.7 | vs |
| 6.9 | s |
| 8.3 | w |
| 16.6 | vs |

2. The magnesium salt of S-omeprazole trihydrate according to claim 1, wherein the compound is in a highly crystalline form.

3. The magnesium salt of S-omeprazole trihydrate according to claim 1, wherein the compound is in a stable form.

4. A process for the preparation of the magnesium salt of S-omeprazole trihydrate according to any of claims 1, 2 or 3 which comprises treating a magnesium salt of S-omeprazole any other form with water.

5. A process for the preparation of the magnesium salt of S-omeprazole trihydrate according to any of claims 1, 2 or 3 which comprises the following steps:

a) mixing a potassium salt of S-omeprazole with an organic solvent;

b) converting the potassium salt of S-omeprazole into a corresponding magnesium salt of S-omeprazole by treating the potassium salt with a magnesium source;

c) precipitating the magnesium salt of S-omeprazole by addition of a non-solvent;

d) isolating the obtained magnesium salt of S-omeprazole;

e) treating the obtained magnesium salt of S-omeprazole with water, and

f) isolating and drying the obtained magnesium salt of S-omeprazole trihydrate

6. The process according to claim 5, wherein the organic solvent of step a) is methanol.

7. The process according to claim 5, wherein the non-solvent of step c) is acetone.

8. The process according to claim 5 wherein steps a) to e) are replaced by the following single step: converting the potassium salt of S-omeprazole into a corresponding magnesium salt of S-omeprazole by treating the potassium salt with a magnesium source in water.

9. The process according to claim 5, wherein the magnesium source is magnesium sulfate.

10. The process according to claim 8, wherein the magnesium source is magnesium sulfate.

11. A pharmaceutical composition comprising the magnesium salt of S-omeprazole trihydrate according to any of claims 1, 2 or 3 as active ingredient and a pharmaceutically acceptable carrier.



12. A method of treating a gastric acid related condition which method comprises administering to a subject suffering from said condition a therapeutically effective amount of the magnesium salt of S-omeprazole trihydrate according to any of claims 1, 2 or 3.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

# CERTIFICATE OF CORRECTION

PATENT NO. : 6,369,085 B1
DATED : April 9, 2002
INVENTOR(S) : Cotton et al.



It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Item [22] PCT Filed, delete "**May 5, 1998**" and insert therefor -- **May 25, 1998** --.

Column 10,
Line 42, insert -- of -- after "S-omeprazole".

Signed and Sealed this

Eighth Day of April, 2003

JAMES E. ROGAN
*Director of the United States Patent and Trademark Office*

**EXHIBIT B**

**FINAL OFFICE ACTION (08/10/2006)**

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/672,936 | 09/25/2003 | Hanna Cotton | 1103326-0502 CON. | 9504 |

7470 7590 08/10/2006

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| EXAMINER | |
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| AULAKH, CHARANJIT | |
| **ART UNIT** | **PAPER NUMBER** |
| 1625 | |

DATE MAILED: 08/10/2006

11/10/06
2/10/07

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/672,936 | COTTON ET AL. | |
| | Examiner | Art Unit | |
| | Charanjit S. Aulakh | 1625 | |

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *19 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1 and 2* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 2* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/12, 5/22/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. According to paper filed on May 19, 2006, the applicants have canceled claims 14, 17 and 18.

2. Claims 1 and 2 are now pending in the application.

### *Response to Arguments*

3. Applicant's arguments filed on May 19, 2006 have been fully considered but they are not persuasive regarding statutory double patenting. The examiner does not agree with the applicants arguments that the scope of instant claims is different than the scope of claims 1 and 2 of the cited patent. The instant claims as well as the claims of the cited patent are identical and directed to magnesium salt of S-omeprazole trihydrate. The applicants have not provided any evidence to show that the peaks in X-ray differactogram of instant claims are different than those of the peaks of the cited patent.

### *Conclusion*

4. Rejection of claims 1 and 2 under 35 U.S.C. 101 is maintained for the reasons of record.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charanjit S. Aulakh whose telephone number is (571)272-0678. The examiner can normally be reached on Monday through Friday, 8:30 A.M. to 5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thomas McKenzie can be reached on (571)272-0670. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

C. S. Aulakh

Charanjit S. Aulakh
Primary Examiner
Art Unit 1625

PTO/SB/08A (08-03)



Substitute for form 1449/PTO

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

| Complete if Known | |
|---|---|
| Application Number | 10/672,936 |
| Filing Date | September 25, 2003 |
| First Named Inventor | Hanna Cotton |
| Art Unit | 1625 |
| Examiner Name | Charanjit Aulakh |
| Attorney Docket Number | 1103329-0502 CON |

## U.S. PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Document Number<br>Number-Kind Code[2] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages/Figures Appear |
|---|---|---|---|---|---|
| CA | | US 6,677,455 | 01-13-2004 | Kronstrom et al. | |
| CA | | US 6,747,155 | 06-08-2004 | Kronstrom et al. | |

## FOREIGN PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Foreign Patent Document<br>Country Code[3]-Number[4]-Kind Code[5] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear | T[6] |
|---|---|---|---|---|---|---|
| CA | | IN 1344/DEL/98 | | | | |
| CA | | DE 4 035 455 | | | | |

## NON PATENT LITERATURE DOCUMENTS

| Examiner Initials* | Cite No. | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T |
|---|---|---|---|
| CA | | Opposition filed by Ranbaxy Laboratories Limited against Indian Patent Application Number 1344/DEL/98 | |
| CA | | Opposition filed by Torrent Pharmaceuticals Limited against Indian Patent Application Number 1344/DEL/98 | |
| CA | | X-ray powder diffraction pattern of Mg-salt of S-omeprazole trihydrate depicted by Torrent obtained by method of WO 94/27988 | |
| CA | | NDA 21-153/S-020 for Nexium®(esomeprazole magnesium) Delayed Release Capsule | |
| CA | | NDA 21-153/21-154 entitled "Medical Review(s)" | |
| | | | |
| | | | |
| | | | |

| Examiner Signature | AULAKH | Date Considered | 8/7/08 |
|---|---|---|---|

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORM TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

PTO/SB/08A (08-03)
Approved for use through 07/31/2006. OMB 0651-0031 U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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Substitute for form 1449/PTO

# INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 1

| Complete if Known | |
|---|---|
| Application Number | 10/672,936 |
| Filing Date | September 25, 2003 |
| First Named Inventor | Hanna Cotton |
| Art Unit | 1625 |
| Examiner Name | Charanjit Aulakh |
| Attorney Docket Number | 1103329-0502 CON |

## U.S. PATENT DOCUMENTS

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## FOREIGN PATENT DOCUMENTS

| Examiner Initials* | Cite No.[1] | Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known) | Publication Date MM-DD-YYYY | Name of Patentee or Applicant of Cited Document | Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear | T[6] |
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## NON PATENT LITERATURE DOCUMENTS

| Examiner Initials* | Cite No. | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published. | T |
|---|---|---|---|
| CA | | Statement with Exhibits A-C on Behalf of the Applicant, AstraZeneca AB, to the Opposition filed by Ranbaxy Laboratories Limited against Indian Patent Application Number 1344/DEL/98 | |
| CA | | Statement with Exhibits A-D on Behalf of the Applicant, AstraZeneca AB, to the Opposition filed by Torrent Pharmaceuticals Limited against Indian Patent Application Number 1344/DEL/98 | |
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| | | | |
| Examiner Signature | | AULAKH | Date Considered 9/7/06 |

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3]Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6]Applicant is to place a check mark here if English language Translation is attached. This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORM TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

**EXHIBIT C**

**PRELIMINARY AMENDMENT (11/12/1999)**

 1103326-0502

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| Applicants | : Cotton et al. |
| Serial No. | : 09/077,719 |
| Filed | : June 8, 1998 |
| For | : NOVEL FORM OF S-OMEPRAZOLE |
| Examiner | : J. Fan |
| Group Art Unit | : 1614 |

**CERTIFICATE OF TRANSMISSION UNDER 37 C.F.R. 1.8**

I hereby certify that this paper is being facsimile transmitted to the U.S. Patent and Trademark Office on November 12, 1999 at the facsimile number 703-308-4734.

John M. Genova — 32,224
Attorney Name — PTO Reg. No.

John M Genova — 11/12/99
Signature — Date of Signature

Assistant Commissioner for Patents
Washington, D.C. 20231

**ATTENTION**: Examiner Jan Fan

**FACSIMILE NO**: 703-308-4734

**DATE**: November 12, 1999

**PAGES**: **5**

Assistant Commissioner for Patents
Washington, D.C. 20231

**PRELIMINARY AMENDMENT**

Sir:

Applicants submit this Preliminary Amendment to place the claims in conformance with U.S. patent practice.

**Please amend the claims as follows:**

**Cancel claim 15:**

**Amend claims 2-14 and 16 as follows:**

2. (Amended) The magnesium salt of S-omeprazole trihydrate according to claim 1, wherein the compound is in a [characterized by being] highly crystalline form.

In claim 3 at line 1, after "claim 1," insert -- wherein the compound is --, and at line 2, delete "." and insert therefor -- : --.

In claim 4 at line 1, after "1-3" insert -- or 17 --.

In claim 5 at line 2, after "1-3" insert -- or 17 --; at line 5 in step b), delete "said"; and at line 9 in step f), after "the" insert -- obtained -- and delete "thus obtained".

6. (Amended) The [A] process according to claim 5, wherein the [said] organic solvent of [used in] step a) is methanol.

7. (Amended) The [A] process according to claim 5 [claims 5-6], wherein the [said] non-solvent of [used in] step c) is acetone.

8. (Amended) The [A] process according to claim 5 wherein steps a) to e) are replaced by the following single step: [; i)] converting the potassium salt of S-omeprazole into a corresponding magnesium salt of S-omeprazole by treating the [said] potassium salt with a magnesium source in water.

9. (Amended) The [A] process according to claim 5 or 8 [claims 5-8], wherein the [said] magnesium source [used in step b) of claims 5-7 or step i) of claim 8] is magnesium sulfate.

In claim 10 at line 1, delete "a" and insert therefor -- the --; at lines 1 and 2, delete "to be used in any of claims 5-9, which process comprises" and insert therefor -- of claim 5, comprising --; at line 6, after "source;" insert -- and -- ; and at line 7, after "the" insert -- obtained -- and delete "thus obtained".

11. (Amended) The [A] process according to claim 10, wherein the [said] organic solvent of [used in] step a) is toluene.

12. (Amended) The [A] process according to claim 10 or 11 [any of claims 10-11], wherein the [said] potassium source of [used in] step b) is methanolic potassium methoxide or methanolic potassium hydroxide.

In claim 13 at line 1, delete "Potassium" and insert therefor -- The potassium --; and after "claim 10" insert -- , wherein the compound is --; and at line 2, delete "." and insert therefor -- : --.

14. (Amended) A pharmaceutical composition comprising the magnesium salt of S-omeprazole trihydrate according to any of claims 1-3 or 17 as active ingredient and [in association with] a pharmaceutically acceptable carrier [and optionally other therapeutic ingredients].

16. (Amended) A method of treating a gastric acid related condition which method comprises administering to a subject suffering from said condition a therapeutically effective amount of the magnesium salt of S-omeprazole trihydrate according to [defined in] any of claims 1-3 or 17.

**Add new claims 17 and 18:**

17. The magnesium salt of S-omeprazole trihydrate according to claim 1, wherein the compound is in a stable form.

18. The pharmaceutical composition according to claim 14 wherein the composition further comprises other therapeutic agents.

## REMARKS

The pending claims upon entry of this Preliminary Amendment are 1-14and 15-18. The amendments place the claims in accordance with U.S. patent practice. Support for new claim 17 is found in the specification at page 3, line 11-13. New claim 18 contains an embodiment that was deleted from claim 14. Applicants submit that no new matter has been introduced by any of the amendments or new claims.